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Nitric oxide, cytochrome c and mitochondria.

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Nitric oxide (NO) and its derivative, peroxynitrite (ONOO-), inhibit mitochondrial respiration, and this inhibition may contribute to both the physiological and cytotoxic actions of NO. Nanomolar concentrations of NO rapidly and reversibly inhibited cytochrome oxidase in competition with oxygen, as shown with isolated cytochrome oxidase, mitochondria, brain nerve terminals and cells. Cultured astrocytes and macrophages activated (by cytokines and endotoxin) to express the inducible form of NO synthase produced up to 1 microM NO, and inhibited their own respiration and that of co-incubated cells via reversible NO inhibition of cytochrome oxidase. NO-induced inhibition of respiration in brain nerve terminals resulted in rapid glutamate release, which might contribute to the neurotoxicity of NO. NO inhibition of cytochrome oxidase is reversible; however, incubation of cells with NO donors for 4 hours resulted in an inhibition of complex I, which was reversible by light and thiol reagents and may be due to nitrosylation of thiols in complex I. NO also caused the acute inhibition of catalase, stimulation of hydrogen peroxide production by mitochondria, and reaction with hydrogen peroxide on superoxide dismutase to produce peroxynitrite. Peroxynitrite inhibited complexes I, II and V (the ATP synthase), aconitase, creatine kinase, and increases the proton leak in isolated mitochondria. Peroxynitrite also caused opening of the permeability transition pore, resulting in the release of cytochrome c, which might then trigger apoptosis. Hypoxia/ischaemia also resulted in an acute reversible inhibition of cytochrome oxidase. Heart ischaemia caused the release of cytochrome c from mitochondria into the cytosol, and at the same time caspase-3-like-protease activity was activated in the cytoplasm. Addition of cytochrome c to non-ischaemic cytosol also caused activation of this protease activity, suggesting that caspase activation and consequent apoptosis is at least partly a result of this cytochrome c release.

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